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Autoimmune syndrome induced by breast implants

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ABSTRACT

Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) is a catch-all name for immunologically-based disorders that develop in genetically predisposed persons after exposure to adjuvants such as silicone breast implants. This article summarizes the existing literature on ASIA, focusing on the link between breast implants and the development of autoimmune diseases. Breast implants have grown in popularity in cosmetic surgery since the 1960s, but their use offers significant health risks, such as inflammatory responses and autoimmune problems. The study clarifies research findings on the pathophysiology of ASIA, focusing on the impact of silicone leaks on the immune system and infiltration into surrounding tissues. It intensively examines the processes that cause foreign body reactions and the potential function of adjuvants in triggering the immune response. Review focuses on silicone mobility and the production of bacterial biofilms, both related to prolonged inflammatory reactions. The findings suggest that more research into implant operation techniques is needed to improve understanding of the risks and provide safer choices for patients. The authors underline the importance of raising patient and professional knowledge about the possible hazards of breast implants, as well as encouraging greater research into silicone-free breast reconstruction techniques.

Keywords: Autoimmune/inflammatory syndrome induced by adjuvants, silicone breast implants, breast implant illness

1. INTRODUCTION

Breast augmentation is one of the most popular plastic surgery procedures. Initially, these operations were performed on women after mastectomy, but today, they are primarily carried out for aesthetic reasons. According to the International Society of Aesthetic Plastic Surgery (ISAPS), in 2022, 2,174,616 breast augmentation procedures were performed worldwide. Since the 1960s, breast augmentation surgery has enjoyed immense popularity among patients

and remains one of the most frequently chosen surgical procedures. Breast implants vary by surface (smooth or textured), fill (silicone gel or saline), and shape (round or anatomic). They are used for cosmetic augmentation, post-mastectomy reconstruction, correcting congenital deformities, and transgender surgery (Kaderbhai et al., 2021).

The specialist physician's role is vital in the decision-making process, as it ensures that the selected method most effectively addresses the patient's needs and reduces the likelihood of complications (Medor et al., 2023). This procedure improves mental health and higher self-esteem for many patients, positively affecting their social and professional relationships (Jawanrudi et al., 2022). The use of silicone breast implants (SBI) was undoubtedly a breakthrough in aesthetic surgery. Cronin and Gerow were the first to achieve this 1962 by placing silicone gel in an elastomer shell. Silicone, considered a biologically inert material, seemed ideal for such an application. Since their introduction, numerous questions have been raised about the safety of breast implants (Cohen-Tervaert et al., 2017).

Many researchers have expressed concerns about a potential link between silicone breast implants and immune system abnormalities, which may contribute to the development of autoimmune diseases and anaplastic large-cell lymphoma (Cohen-Tervaert et al., 2017). In response to these concerns, breast implant standards and regulations have been introduced to minimize risk. These standards include production and presenting quality control certificates (Colaris et al., 2017). Autoimmune diseases have been associated not only with breast implants but also since the 1990s; alarming reports have also emerged regarding their possible connection to vaccines.

The hepatitis B vaccine has been most frequently linked to conditions such as erythema nodosum, polyarthritis, immune thrombocytopenia, myasthenia, and many others (Seida et al., 2023). These findings prompted further research, suggesting that adjuvants may predispose individuals to the development of autoimmune diseases. Based on this, in 2011, Shoenfeld and colleagues introduced the concept of ASIA (Shoenfeld and Agmon-Levin, 2011). This article focuses on a detailed review of the current medical literature on ASIA. We aimed to determine whether there are associations between breast implants and the occurrence of autoimmune diseases within the framework of ASIA.

2. METHODOLOGY

Keywords like "Autoimmune/inflammatory syndrome induced by adjuvants", "silicone breast implants", and "breast implant illness" were used to search easily accessible medical sources like PubMed and ScienceDirect. The review included articles published between 1997 and 2024 that were chosen based on abstracts and titles to examine the effects of autoimmune syndrome induced by breast implants. The review includes clinical research, systematic reviews, and meta-analyses on Patients with breast implants who experienced adverse symptoms after breast surgery. Excluded were publications written in languages other than English.

3. ASIA

ASIA (Autoimmune/Inflammatory Syndrome Induced by Adjuvants) is an umbrella term that describes immunologically-based diseases. These diseases are likely to develop in genetically predisposed patients following exposure to an external factor known as an adjuvant. A characteristic feature of this syndrome is the loss of immune system control, with the potential development of autoantibodies and symptom relief after removing the causative factor (Borba et al., 2020). Adjuvants are auxiliary substances that, although not typically immunogenic themselves, modulate the immune response to a specific antigen. Increasing the strength, scope, and duration of the immune response can also reduce the need for multiple booster doses in vaccinations (Reed et al., 2013; Verma et al., 2023).

Adjuvants impact both adaptive and innate immune system branches by activating Toll-like receptors (TLR), NOD-like receptors (NLR), and C-type lectin receptors. These receptors are activated, producing cytokine, promoting chemotaxis of dendritic cells, and activating antigen-presenting cells, thereby enhancing the adaptive immune response to the antigen (Watad et al., 2017). Examples of adjuvants include aluminum compounds, squalene emulsions, paraffin, silicone, and microbial fragments. In recent years, it has become clear that medical implants, including breast implants, injectable agents used in aesthetic medicine, mineral oils, cosmetics, and many others, can trigger immune responses by acting as adjuvants, leading to serious health complications (Cohen-Tervaert et al., 2021). The diagnosis of ASIA requires the fulfillment of at least two primary criteria or one primary criterion with two minor criteria (Seida et al., 2023) (Table 1).

Table 1 The diagnostic criteria for ASIA syndrome

Major Criteria	Minor Criteria
1. Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before the onset of clinical symptoms.	1. Appearance of antibodies directed against the suspected adjuvant.
2. Presence of typical clinical symptoms:	2. Secondary clinical symptoms (e.g., irritable bowel syndrome, interstitial cystitis, etc.).
a. Muscle pain, myositis, or muscle weakness.	3. Development of an autoimmune disease (e.g., multiple sclerosis, systemic sclerosis).
b. Joint pain and/or arthritis.	4. Specific human leukocyte antigens (HLA DRB1, HLA DQB1).
c. Chronic fatigue, unrefreshing sleep, or sleep disturbances.	-
d. Neurological symptoms (especially related to demyelination).	-
e. Cognitive impairment, memory loss.	-
f. Fever.	-
3. Typical histological findings from biopsies of affected organs.	-
4. Improvement in symptoms after the removal of the causative factor.	-

Source: Seida et al., (2023) "Autoimmune/Inflammatory Syndrome Induced by Adjuvants". *Clin Exp Immunol*, vol. 213, no. 1, 2023, pp. 87-101. doi:10.1093/cei/uxad033.

Who is prone?

Autoimmune diseases are chronic disorders with a diverse range of symptoms. The body attacks and destroys its own tissues, mistakenly identifying them as foreign. Due to their chronic nature and high treatment costs, it is decided first to identify groups of people predisposed to developing these diseases. It is believed that the occurrence of autoimmune diseases requires the interaction of genetic and environmental factors. Studies on the prevalence of autoimmune diseases in families suggest that members of the same family may share genes that increase their susceptibility to developing these diseases (Borba et al., 2020). Additionally, genetic factors predisposing individuals to ASIA (Autoimmune/Inflammatory Syndrome Induced by Adjuvants) are thought to include epigenetic elements and specific HLA antigens (Seida et al., 2023).

The most commonly associated genes with this syndrome are HLA-DRB1, HLA DQB1, HLA-B27, and PTPN22. Identifying an external factor is usually not a problem. The influence of smoking, obesity, exposure to silicone, solvents, asbestos, infections, vaccines, and chemotherapy has been documented (Smatti et al., 2019; Pollard et al., 2021). A role in the development of autoimmune diseases is also attributed to vitamin D deficiency (Colaris et al., 2017). In the context of breast implants, molecular mimicry is considered the primary mechanism leading to the development of autoimmune diseases. This phenomenon involves the similarity between self-antigens and foreign antigens that mimic them, potentially activating autoreactive T and B cells (Rojas et al., 2023).

However, it is unlikely that molecular mimicry is the only mechanism at play. Central tolerance disruptions, epitope spreading, and/or constant antigenic stimuli may also be significant factors. Goren et al., (2015) identified several groups of patients predisposed to developing silicone-induced ASIA: 1) patients with documented autoimmune reactions following exposure to adjuvants, 2) patients with diagnosed autoimmune diseases, 3) patients with allergic/atopic diseases, and 4) patients with family history of genetic diseases.

Symptoms

Studies suggest that regardless of the method of breast augmentation, patients report overall satisfaction with their quality of life, but despite numerous advances, they do have a downside. Despite the emphasis on improving surgical techniques and implant biocompatibility, they are still associated with some complications. One group of complications can be classified as local, including symptoms such as pain, swelling, redness, capsular contracture (CC), painful enlargement of lymph nodes, and skin changes (Pagani et

al., 2022). Breast implants placed in the body lead to an inflammatory reaction known as a foreign body response (FBR), which results in the formation of a fibrous capsule, isolating the foreign material from the rest of the body.

The formation of a fibrous capsule is a physiological response to the foreign body. Still, chronic inflammation may lead to capsular contracture (CC) through the tightening of collagen fibers, which can deform the breast and cause significant pain (Safran et al., 2021). Silicone released in the event of implant rupture or gradually seeping through an intact shell in a process known as "gel bleed" can migrate to various parts of the body, forming hardened granulomas. These typically form in the lymph nodes, skin, or breasts and much less frequently in the lungs, lower limbs, liver, and spleen. Silicone migration occurs slowly, which explains why symptoms can take 5-6 years to appear after implantation (Elahi et al., 2022). Since the released silicone from breast implants leads to increased exposure and higher risks of complications, it is recommended that patients with breast implants undergo regular check-ups, even in the absence of clinical symptoms.

MRI is recommended to detect implant rupture, while mammography is contraindicated as there have been cases of implant damage during the procedure (Cohen-Tervaert et al., 2022). Ultrasonographic imaging is recommended for diagnosing silicone lymphadenopathy, with the characteristic "snowstorm" appearance having high sensitivity and specificity (Pelegrina-Perez et al., 2024). Women with silicone breast implants (SBI) may present with enigmatic, nonspecific systemic symptoms such as cognitive dysfunction, rash, difficulty concentrating, joint pain, brain fog, fever, dry mouth (sicca), visual disturbances, muscle pain, memory loss, dry eyes, fatigue, and Raynaud's phenomenon (Cohen-Tervaert et al., 2022; Suh et al., 2022; Cohen-Tervaert et al., 2023). These symptoms are referred to as "breast implant illness" (BII), which is a classic example of ASIA syndrome, in which silicone acts as an adjuvant.

Often, a tilt table test in patients with SBI confirms POTS (postural orthostatic tachycardia syndrome). This syndrome is characterized by dizziness, balance issues, irregular heartbeat, and sometimes chest pain (Cohen-Tervaert et al., 2022). Patients with SBI often experience systemic symptoms similar to chronic fatigue syndrome (CFS/ME). These symptoms include fatigue that does not improve with rest, sleep disturbances, and cognitive impairments, such as problems with memory and concentration or difficulty finding the right words during speech (Cohen-Tervaert et al., 2022). It is crucial to remember that symptoms can have many causes, such as perimenopause, childbirth, medication side effects, stress, or even lifestyle changes. A holistic approach to the patient and a comprehensive assessment can be crucial in the course of treatment.

Additionally, some patients may experience neurological symptoms, such as cerebral ischemia or symptoms similar to multiple sclerosis (Cohen-Tervaert et al., 2017). Up to 50% of patients with SBI may experience hearing impairment, with tinnitus being the most common issue, which usually resolves after implant removal (Tocut et al., 2022). Early detection and treatment are crucial because these disruptions may be linked to depression, sleep issues, or a general reduction in quality of life (Greenbaum et al., 2023). SBI has the potential to exacerbate asthma in women. Causes are not yet fully understood, but silicone contained in implants may activate specific immune pathways, which could aggravate asthma symptoms (Simon et al., 2023). Although silicone breast implants can cause adverse psychiatric symptoms, the incidence of such symptoms among women with implants does not differ from that of the general population (Suri and Billick, 2024).

Epidemiological studies on the safety of patients using silicone breast implants (SBI) have shown an increased risk of Sjögren's syndrome, scleroderma, rheumatoid arthritis, miscarriages, and melanoma. However, no association was found with brain cancer or suicide (Colaris et al., 2022). A recent sizeable retrospective study demonstrated a significant association between SBI and sarcoidosis, Sjögren's syndrome, and systemic sclerosis (Watad et al., 2018). Autoimmune dysautonomia associated with SBI has also been observed. It is caused by reduced levels of IgG antibodies targeting G protein-coupled receptors (GPCRs) of the autonomic nervous system, such as adrenergic, muscarinic, endothelin, and angiotensin receptors. This condition can lead to symptoms such as severe fatigue, widespread pain, palpitations, dry mouth and eyes, depression, and hearing loss (Talalai et al., 2023).

Recently, a link between the dysregulation of IgE antibodies targeting GPCRs of the autonomic nervous system and the occurrence of allergies in women with SBI was also described. The above systemic symptoms are not limited to silicone breast implants. Studies have not shown differences in the prevalence of these symptoms between women using SBI and those with saline-filled implants (Suh et al., 2022). Furthermore, Alijotas-Reig et al., (2018) demonstrated that other biomaterials besides silicone, such as polyalkylimide, polylactic acid, and hyaluronic acid, can cause symptoms similar to those seen in patients with SBI.

Pathophysiology

Silicone was previously considered to be a neutral, harmless material that did not provoke an immune response, which explains its widespread use in everyday products and in medicine. It is found in numerous products, such as breast and testicular implants, catheters, heart valves, and many others. However, the theory of silicone's "inertness" in the body is now being seriously questioned. A biocompatibility study of silicone implants conducted on a 3D human skin model showed that silicone is not cytotoxic but induces a chronic inflammatory response (Nuwayhid et al., 2024). A large retrospective study involving 24,651 women with silicone breast implants (SBI) and 98,604 women without SBI found a statistically significant association between autoimmune diseases and SBI.

The highest associations were reported for sarcoidosis (OR 1.98 (95% CI 1.50–2.60)), systemic sclerosis (OR 1.63 (95% CI 1.26–2.11)), and Sjögren's syndrome (OR 1.58 (95% CI 1.26–1.97)) (Watad et al., 2018). Several probable mechanisms could explain the link between breast implants and autoimmune diseases. Implanted breast implants lead to a series of inflammatory and repair processes known as the foreign body response (FBR). This is a physiological reaction by the body aimed at isolating the foreign material by surrounding it with a collagen capsule (Sheikh et al., 2015). This process begins with interactions between blood and the biomaterial, where plasma components are adsorbed onto the implant surface. The properties of the biomaterial—such as roughness, hydrophobicity, surface field, and composition—can influence protein adsorption and, subsequently, the intensity of the inflammatory process (Sheikh et al., 2015).

Therefore, advanced research is being conducted to modify the surface of breast implants to achieve the highest possible biocompatibility and integration with the body (Sheikh et al., 2015). However, the acute response often becomes chronic, where the intense inflammatory reaction never fully resolves. This chronic state is characterized by the presence of macrophages and foreign body giant cells (FBGC) (Foroushani et al., 2022). M1 macrophages, also known as "classically activated" macrophages, are key elements of the body's response to tissue injury or infection. M1 macrophages promote inflammation by releasing pro-inflammatory cytokines such as IL-6, IL-12, TNFα, reactive oxygen species, and antimicrobial peptides (Sheikh et al., 2015). Moreover, they have strong phagocytic capabilities and can present antigens to helper T cells (Th1) (Martin and Garcia, 2021).

When macrophages encounter too large particles, they can fuse to form multinucleated giant cells (FBGC). This process is induced by IL-4 and IL-13, which increase the expression of mannose receptors on fusing macrophages. As the size of the cells increases, so does their ability to degrade the extracellular matrix, playing a key role in the degradation of biomaterials (Eslami-Kaliji et al., 2023). On the Other Hand, M2 macrophages are characterized by releasing anti-inflammatory mediators and growth factors, which support tissue healing. They arise through innate or adaptive mechanisms by releasing IL-4 from mast cells or IL-4 and IL-13 produced by Th2 cells (Sheikh et al., 2015). M1 macrophages dominate throughout all stages of FBR, and chronic inflammation may be responsible for its progression.

Additionally, it has been found that in 60% of patients with SBI, the population of helper T cells significantly exceeds the population of regulatory T cells (Yang et al., 2022). Foreign body giant cells (FBGC), which release reactive oxygen species (ROS) and lytic enzymes, can play a key role in damaging the elastomer shells of implants, leading to ruptures (Sheikh et al., 2015). Studies have shown that low molecular weight fillers increase the risk of implant rupture through shell swelling (Gangineni et al., 2023). When an implant ruptures, the filler material typically remains within the intact fibrous capsule surrounding the implant. However, in some cases, rupture leads to silicone leakage beyond the capsule, resulting in the migration of silicone particles into surrounding or distant tissues. This can lead to a siliconoma forming, which results from a foreign body reaction (Elahi et al., 2022).

Silicone particles that reach lymph nodes can exhibit adjuvant effects (Colaris et al., 2022). Microscopic silicone droplets can pass through the intact surface of the implant, a phenomenon known as "gel bleed". Despite using highly cohesive silicone gel, which theoretically resolves this problem, experimental models have shown that gel bleed may still occur (Errico et al., 2021). Siliconoma formation has generally been associated with SBI, but silicone migration and granuloma formation cases have also been reported in saline implants (Pelegrina-Perez et al., 2024; Azahaf et al., 2024). The interaction of free silicone with Toll-like receptors and the NALP3 inflammasome of phagocytic cells leads to continuous stimulation of the inflammatory response, which is likely a key factor in the pathogenesis of ASIA (Caravantes-Cortes et al., 2020). Apart from the leading pathophysiological theory linking the onset of Breast Implant Illness (BII) with silicone leakage, some researchers suggest other mechanisms of pathogenesis.

Two of the most popular theories are characterizing BII as a psychosomatic syndrome or emphasizing the presence of bacterial biofilm on breast implants and identifying it as the leading cause of BII. Breast implant-related illness is often classified as a psychosomatic disorder, as the symptoms attributed to implants cause disability to a much greater extent than can be seen from

abnormal tissue changes (Suri and Billick, 2024). This suggests the potential success of a psychiatric approach to treatment. The biofilm theory also appears promising, as biofilm can form on all implants, including breast implants. Its protective properties for bacteria make eradication difficult and lead to a chronic inflammatory response (Ajdic et al., 2016). Furthermore, studies have shown that chronic inflammation is triggered by biofilm and is associated with the occurrence of capsular contracture (CC) and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) (Ajdic et al., 2016; Khan et al., 2023).

Comparison of Breast Implants

Over 60 years of using silicone-based breast implants (SBI) have resulted in the development of six generations of these implants and several well-known safety crises associated with their use (Deva et al., 2019). Silicone is a silicon, oxygen, carbon, and hydrogen polymer. Its physical properties depend on the length of the polymer chains and the degree of cross-linking. Liquid silicones are characterized by short chains and minimal crosslinking, whereas longer chains and greater crosslinking result in silicone with higher viscosity and cohesion. SBI are two-component products consisting of a liquid silicone gel that forms the core and an elastomer shell with rubber-like properties. The structure of elastomers is similar to that of silicone gel, but it is much more crosslinked and contains less fluid, which allows for forming a durable and flexible outer coating (Kaoutzanis et al., 2019).

The first generation of breast implants featured a smooth, durable elastomer shell and a dense filler material. Dacron patches were placed on the posterior surface to limit implant migration. Despite the durability of these implants and a low rupture rate, they felt unnatural and, in most cases, led to calcifications (Hillard et al., 2017). In response to these problems, second-generation implants were developed with a much thinner shell and a less dense filler. The patches were also eliminated. These modifications allowed for a softer, more natural feel, but the thinner shell resulted in ruptures in 60% of cases, and the low-cohesion gel with sparse crosslinking contributed to frequent leakage through the shell, known as "silicone bleeding" (Hillard et al., 2017). The introduction of third-generation implants was designed to tackle the issues of frequent ruptures and silicone bleeding.

To address the problems of frequent rupture and bleeding of silicone, third-generation implants were introduced, featuring a coherent gel with enhanced cross-linking and multilayer coatings. As a result, implant lifespan was significantly increased and the risk of calcification decreased, but the complication rate remained high. In particular, concerns were raised about the potential link between connective tissue disorders and SBI. Consequently, in 1992, the Food and Drug Administration (FDA) temporarily restricted third-generation silicone gel implants in the U.S. market (Kaoutzanis et al., 2019). The fourth generation introduced surface texturing, as it was noted that it could mitigate or reduce the frequency of calcifications.

Subsequent generations introduced additional features: the fifth generation included an anatomically shaped implant and highly cohesive gel, while the sixth generation was equipped with a biocompatible shell and a rheological gel capable of changing its consistency in response to applied forces, allowing it to mimic the shape and feel of a natural breast (Foroushani et al., 2022). In response to silicone breast implants (SBI), saline implants were developed, which are characterized by reduced surgical trauma, as an empty implant can be inserted through a relatively small incision and then filled with saline once it is in place. However, this solution has several drawbacks: firstly, saline implants tend to rupture and deflate relatively quickly (although the leakage of saline is far less dangerous than the leakage of silicone gel).

Moreover, these implants mimic the natural breast less effectively—they are more challenging and stiffer (Azahaf et al., 2024; Kaoutzanis et al., 2019). Since it has been demonstrated that implant volume plays a role in the frequency of complications, especially when there is a higher implant-to-BMI ratio or an increased implant volume relative to the patient's height, attempts have been made to enlarge breasts using autologous fat alone or through a hybrid approach that allows the use of a smaller implant combined with fat grafting (Medor et al., 2023). However, despite high expectations, the final result of these procedures was unstable, as the transplanted fat quickly underwent resorption (Yanaga et al., 2023).

A recently developed innovative breast reconstruction technique using cultured mature adipocytes (CMA) mixed with a conditioned medium has proven to be both safe and durable (Yanaga et al., 2023). This may be a promising direction for minimizing the risk of ASIA syndrome in high-risk patients. In 2011, the FDA identified a possible association between breast implants and a rare type of T-cell lymphoma known as Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) (Kaoutzanis et al., 2019). Studies revealed that textured implants (as opposed to smooth ones) are strongly linked to this malignancy, and chronic inflammation, likely caused by infection and biofilm formation, drives its development (Khan et al., 2023).

4. DISCUSSION

Consideration of Various Hypotheses on the Etiology of Breast Implant-Related Diseases

Since the 1960s, scientific research has examined the causes of disorders linked to breast implants, including Breast Implant Illness (BII), which is a complicated and multidimensional problem (Bird and Niessen, 2022). There are many theories on causes, mechanisms, psychological impacts, and how these factors interact in discussing this topic. One of the main reasons that questions related to this topic are continually raised is the growing belief that silicone in implant products may act as an adjuvant, activating autoinflammatory processes associated with the development of autoimmune diseases (Shoenfeld and Agmon-Levin, 2011; Shoenfeld and Maślińska, 2013).

Even though breast implants are among the most thoroughly researched medical products and few have undergone a similar level of scrutiny Mahić et al., (2020), there remains a significant lack of trust both from the medical community and from patients. This is partly due to the risk of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) and the lack of definitive answers to very complex questions and concerns related to the more than 56 sets of BII symptoms reported by SBI patients (Lee et al., 2020). Moreover, Watad et al., (2018) conducted a large cross-sectional study examining whether women with silicone breast implants were more likely to be diagnosed with autoimmune or rheumatic diseases.

Women with silicone breast implants were associated with a higher likelihood of being diagnosed with autoimmune or rheumatic diseases, regardless of whether the breast implant was placed for reconstructive or cosmetic reasons (Suh et al., 2022). The risk ratio for being diagnosed with at least one autoimmune or rheumatic disease was 1.45 (95% CI 1.21-1.73), indicating an increased risk of developing any autoimmune or rheumatic disease among patients with breast implants (Watad et al., 2018). In light of the insufficient understanding of BII pathophysiology, several theories regarding its etiology have been proposed Suh et al., (2022), Cohen-Tervaert et al., (2017) hypothesized that the chronic inflammatory response might result from the migration of silicone gel due to implant "bleeding" and lead to symptoms described in Breast Implant Illness.

Studies suggest that silicone contained in implant products may act as an adjuvant Cohen-Tervaert, (2018), enhancing an antigen-specific immune response and thereby penetrating lymph nodes or the liver, potentially causing chronic inflammation, or reaching the lungs, causing conditions such as acute pulmonary embolism or sarcoidosis (Dijkman et al., 2021; Agilinko et al., 2021; Singh et al., 2018; Teuber et al., 1994). In Ellis et al., (1997) demonstrated that the frequency and intensity of the cellular immune response against collagen I, collagen III, fibrinogen, and fibronectin were higher in women with SBI compared to healthy women from a control group matched for sex and age.

Goldblum R and colleagues found that patients with intense immune responses to silicone implants had increased IgG concentrations in the surrounding tissue and higher levels of antibodies against silicone compared to patients who did not exhibit symptoms after using these medical products (Goldblum et al., 1992). In Kappel et al., (2016) published the results of postmortem studies of a patient who had undergone breast surgery 17 years earlier. The implant had ruptured, and a lymph node biopsy showed a reaction to silicone, which led to numerous clinical complaints consistent with ASIA syndrome. The researchers used transmission electron microscopy and energy-dispersive X-ray microanalysis to measure elemental silicon in the tissue. Silicone material was found in vessels or collagen capsules of various organs, including the brain.

This suggested that small silicone particles (monomer and oligomer) could enter cells and disrupt intracellular metabolic pathways, leading to cellular disturbances and clinical symptoms (Kappel et al., 2016). Others believe that despite confirmed silicone leakage, silicone is still considered biologically neutral. Therefore, there are doubts as to whether silicone implants are indeed the cause of numerous complaints from patients who received them (Spoor et al., 2022). A study conducted on a group of 90 women analyzing the relationship between silicone leakage beyond the implant capsule and breast implant-related diseases shows that while spectroscopy detected the presence of silicone in the liver of some patients, there were no clear, statistically significant correlations between this phenomenon and the occurrence of clinical symptoms such as chronic fatigue, musculoskeletal pain, or autoimmune ailments in patients without silicone leakage.

This study suggests that the implant condition may have marginal significance for clinical symptoms (Gaubitz et al., 2002). Another hypothesis regarding the relationship between bacterial biofilm and breast implants suggests that its formation on the implant's surface may lead to long-term interactions between the host and the pathogen. Such interactions result in chronic inflammation, which may trigger systemic autoimmune symptoms. Due to its complex structure and ability to protect bacteria from the immune system and

antibiotics, biofilm has been linked to numerous biomaterial complications, including capsular contracture and Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Like orthopedic prostheses, bacterial biofilm may be a key factor in long-term complications such as implant loosening or chronic pain (Ajdic et al., 2016; Lee et al., 2020; Ellis et al., 1997).

A study by Lee and colleagues on 50 patients with Breast Implant Illness (BII) symptoms showed that bacterial biofilm was more frequent in patients with BII than in the control group. The most commonly identified bacteria were *Propionibacterium acnes* and *Staphylococcus epidermidis*, known for their ability to colonize biomaterial surfaces and form biofilms on medical implants. Furthermore, the resolution of symptoms in patients following the removal of implants and their surrounding capsules indicates the potential role of biofilm in the pathogenesis of BII. Additional data suggest that antibiotic therapy, such as clarithromycin, could be a promising therapeutic strategy, as demonstrated in treating sarcoidosis linked to *P. acnes* (Ajdic et al., 2016; Lee et al., 2020).

Bartok and colleagues also highlighted a 50% increased incidence of synovial metaplasia of the capsule in patients with BII. This previously demonstrated phenomenon is a key factor in the development of rheumatoid arthritis and supports the assumption that chronic immunological stimulation caused by biofilms may lead to autoimmune diseases. These findings raise the possibility of a link between autoimmune diseases, BII symptoms, and the infectious properties of biofilms, which could lead to new approaches to the prevention and treatment of these problems (Ellis et al., 1997).

Explantation of implants

An essential criterion for ASIA is the observation that both subjective and objective symptoms that appear after the implantation of breast implants (such as chronic fatigue or widespread pain) are often alleviated after their removal. The reduction or resolution of symptoms following implant removal (commonly referred to as "withdrawal") is a key observation in the diagnosis of ASIA and establishing causality. This improvement has been well-documented, for example, in patients with silicone breast implants De-Boer et al., (2017) and in a 33-year-old woman who developed systemic symptoms after a hernia repair surgery and experienced relief after the removal of the surgical mesh (Dias et al., 2021). Since women undergoing explanation report lower satisfaction with their appearance and reduced self-confidence regarding their looks, experts emphasize that implant removal should not be treated as the gold standard of treatment (Suh et al., 2022).

5. CONCLUSIONS

Although most used for aesthetic purposes, breast implants could pose serious health risks. The concerns include inflammatory reactions and the beginning of autoimmune diseases, mainly related to silicone breast implants, which could be adjuvants—activating the immune system and causing autoimmune diseases in predisposed individuals. Pathophysiological studies suggest that events like "gel bleeding" and the translocation of silicone particles across the body could cause ongoing inflammation and start autoimmune reactions. Bacterial biofilm on implants could cause ongoing inflammation and systemic issues, including breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL).

Those who have breast implants may experience a variety of nonspecific systemic symptoms, including neurological issues, myalgia, arthralgia, and chronic fatigue. Usually referred to as "breast implant illness" (BII), these symptoms, especially the removal of implants, bring relief from symptoms; nonetheless, it may compromise patient pleasure with their appearance and self-esteem. Recent findings highlight the critical need for further research into the pathogenic processes associated with Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) and the exploration of alternative breast reconstruction methods. Understanding the potential risks of implants is essential for patients and healthcare professionals. Enhancing awareness of these issues can facilitate informed decision-making and ensure patients receive optimal care tailored to their needs.

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All data sets collected during this study are available upon reasonable request from the corresponding author.

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